

REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

Claims 13-37 and 39-47 are currently pending in the application. Claims 13-24, 34 and 46 have been canceled without prejudice or disclaimer. Claims 25 and 36 have been amended. The forgoing amendments are made to more clearly state the subject matter being claimed.

Support for the amendments to the claims can be found throughout the application as filed. No new matter has been added by the amendments to the specification or the claims.

REJECTIONS

1. Claims 13-24 remain rejected under 35 USC 112, first paragraph.

The Examiner states, "The scope of the claims is interpreted as preventing metastases of cancer by administering effective amount of hyaluroran. Giving the broadest interpretation to the claims, it is the examiner's position that the claims are directed toward the prevention of cancer from invading a particular area:

(a) The evidence submitted is insufficient and there is no statistical data supporting the prevention of cancer evidenced in the broad scope of the claims. While hyaluloran may be effective in sensitizing non-lymphoid tumor cells to, certain antineoplastic agents in vitro and therefore may be useful in treatment of lymphatic cancer, at best such evidence is only a single example of the effectiveness of hyalurolan in cancer treatment and is not supportive of the broad concept of cancer prevention.

(b) Secondly, there is no declaration on file showing evidence of the effectiveness of hyaluoran as effective antineoplastic agent in vivo.

(c) Cancer metastasis invariably involves a complex series of biochemical steps that eventually lead to the re-growth of cancer cells from one site to the other. Simply put, the examiner believes that the following are involved in the process: i.e. tumor invasion is the first step in the complex multi-step process that leads to metastases formation. Following local invasion of adjacent host tissue barriers, the tumor cell must invade the vascular wall or lymphatic channels in order to disseminate. Tumor cells entering the circulation must be able to evade host defenses, survive the mechanical trauma of the blood flow and arrest in the venous or capillary bed of the target organ. Once arrested, the tumor

cells must again invade the vascular wall to enter the organ parenchyma. Finally, the extravasated tumor cell must be able to grow in the "foreign" location different from the tissue of origin in order to initiate a metastatic colony. Simply put, a metastatic tumor cell must possess the capability to traversing all of these indicated steps if not more.

Therefore, based upon this simplified view of metastasis, examiner interpretes the claims and data in examples 2, 4 and Figure 6 as being inadequate to permit broad interpretation that hyaluloran is effective in the preventing metastasis of cellular proliferation--the process indirectly involves the prevention of cancer in a subject because as explained, following colonization of a new site, the tumor cell will have to grow.".

Applicants have canceled claims 13-24, thereby obviating this rejection.

2. Claims 13-37 and 39-47 remain rejected under 35 USC 103(a) as being unpatentable over Harper et al (US 5, 977, 088) in view of Faulk et al (US 5, 827, 834).

The Examiner states, "The claims are directed toward a method of preventing metastasis of cellular proliferative disease (e.g. prostate cancer, ovarian, endocrine et) comprising the step of administering to a subject mammal effective amount of hyaluron (Mol wt of 750, 000-1,500,000 D); wherein the hyaluroran is given in combination with a pharmaceutical carrier or adjuvant (oral, parenteral or topical administration). The claims are also drawn toward administration of chemotherapeutic agent (e.g 5-FU, BCNU or taxane)

Harper et. al. (Patent '088) disclose that effective amounts of pharmaceutical compositions of hyaluronic acid and /or salts, homologues, analogs, derivatives or esters applied to the skin facilitate the transport of medicines and/Or therapeutic agents intradermally into the skin to sites of a pathology and/or trauma to sites of trauma (col. 8, lin 60 and col. 9, lin 60), resulting in successful treatment of the disease or condition at the site of trauma or pathology including basal cell carcinoma, metatatic cancer of the breast to the skin and metoestatic melanoma.

Harper neither specifically teach the use of pharmaceutical compositions with hyaluronic acid for elimination of the onset of metastases of cancer cells to other organs nor does it teach the use of hyaluronic acid immediately before or after the drug administration to overcome drug resistance.

Faulk et. at disclose that administration of combination of antineoplutic agent mixed with hyaluronic acid to a patient who had advanced carcinoma with metastases—the cases disclosed demonstrate effective use of hyaluronic acid and chemotherapeutic to limit tumor metastases (col 13, lin 60, col 14, lin 20-30, col 15 lin 50-65 col 22, lin 25-45; col 29, lin 25, col 30, lin 30-40 and col 35, lin 1-30). Faulk also disclosed the use of hyaluronic acid either before or after the

administration of the antineoplastic agent (col 15, lin 50-65). Faulk alludes to the fact that hyaluronic acid may improve the penetration of the drug through the skin (col 6, lin 60-65).

One of ordinary skill in the art would have been motivated to use a method of administering antineoplastic composition comprising hyaluronic acid and effective agents such as 5-FU to patients in order to obtain inhibition of cell proliferation during treatment of cancer as was disclosed by Patent '088 (col 23, lin 45-67). It would have been obvious to one of ordinary skill in the art at the time the invention was made to add hyaluronic acid taught in Patent '088 to antineoplastic agent in order to obtain the beneficial effect of the antineoplastic agents taught in Patent '834 because the hyaluronic acid at least is generally known to improve the penetration of drugs into the cell. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made by the applicant only as far as it pertains to treatment and not prevention of cancer.".

Applicants have amended independent claims 25 and 36 to limit the administering of a therapeutic effective amount of a composition comprising hyaluronan and a chemotherapeutic agent to oral or parenteral administration. All other claims are dependent from claims 25 or 36. Further , Applicants have canceled claims 23 and 34 which include reference to topical administration.

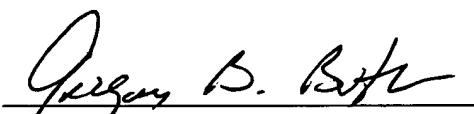
Since the Harper reference relates solely to the topical administration of hyaluronic acid formulations and the claims, as now amended, relate to oral and parenteral administration, Harper is not relevant as a 35 USC 103(a) reference. Withdrawal of the rejection is respectfully requested.

In summary, reconsideration of this application and the allowance of Claims 25-33, 35-45 and 47 of this application are respectfully requested for the reasons stated above.

If there any questions regarding this Amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1105.

Respectfully submitted,


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